Heritage Information Systems, Inc.

Clinical Edit Proposal

Drug/Drug Class:	**Atomoxetine (Strattera™)/ selective norepinephrine re-uptake inhibitor**
Prepared for:	Missouri Medicaid
Prepared by:	Heritage Information Systems, Inc.

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of Strattera™ (atomoxetine) therapy to determine whether this medication should be made available on an open access basis to prescribers, or require prior authorization for use.
Dosage Forms & Manufacturer:	10mg, 18mg, 25mg, 40mg and 60mg capsule Eli Lilly
Summary of Findings:	Strattera™ (atomoxetine) is a selective norepinephrine reuptake inhibitor and is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD). The effectiveness of atomoxetine in the treatment of ADHD has been established in randomized, double-blinded, placebo-controlled studies in children, adolescents and adults. Strattera™ can increase blood pressure and heart rate and should be used with caution in patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease. Unlike other medications used to treat ADHD, this drug is not considered a stimulant and is not a controlled substance.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☐ Appropriate Indications ☐ PA Not Required

Purpose

The purpose of this monograph is to provide a review of Strattera therapy to determine whether this drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guiding appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1,2]

Strattera™(atomoxetine) is a selective norepinephrine reuptake inhibitor and is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD). The effectiveness of atomoxetine in the treatment of ADHD has been established in randomized, double-blind, placebo-controlled studies in children, adolescents and adults. Unlike other medications used to treat ADHD, this drug is not considered a stimulant and is not a controlled substance.

Dosage Form(s)

Strattera™ is available in an oral capsule formulation and is supplied in strengths of 10mg, 18mg, 25mg, 40mg and 60mg.

Manufacturer

Eli Lilly and Company

Indication(s)[1]

Strattera™ is indicated for the treatment of attention deficit/hyperactivity disorder (ADHD) in children, adolescents and adults.

Clinical Efficacy[1,2] (mechanism of action/pharmacology, comparative efficacy)

Strattera™(atomoxetine) is a selective norepinephrine reuptake inhibitor and is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults. The exact mechanism of action is unknown, but may be related to the selective inhibition of the pre-synaptic norepinephrine transport, which is responsible for norepinephrine degradation. Unlike other medications used to treat ADHD, atomoxetine is not considered a stimulant or a controlled substance. The effectiveness of atomoxetine in the treatment of ADHD has been established in randomized, double-blinded, placebo-controlled studies in children, adolescents and adults:

Patient Population	Study Design	Results
Children and adolescents aged 8 to 18 (N = 297)	• 8 week randomized, double-blind, placebo controlled, dose-response, acute treatment study. • Fixed dose of 0.5, 1.2 or 1.8 mg/kg/day or placebo.	• The 2 higher doses of atomoxetine provided statistically significant improvements in ADHD symptoms* compared with the placebo-treated patients. • The 1.8 mg/kg/day atomoxetine dose did not provide additional benefits over that observed with 1.2mg/kg/day. • The 0.5mg/kg/day dose was not statistically superior to placebo.
Children and adolescents aged 6 to16 (N = 171)	• 6 week randomized, double-blind, placebo-controlled, acute treatment study. • Atomoxetine was administered as a single morning dose, titrated on a weight-adjusted basis according to clinical response to a max dose of 1.5mg/kg.day.	• The mean final dose was approximately 1.3mg/kg/day ADHD symptoms* were statistically significantly improved on atomoxetine compared to placebo. • The study shows that atomoxetine is effective when administered a single morning dose.
2 identical studies (N = 147 and N = 144): Children aged 7 to 17	• Randomized, double-blind, placebo-controlled. • Atomoxetine and methylphenidate compared to placebo. • Atomoxetine administered in two divided doses, early morning and late afternoon and titrated on a weight-adjusted basis according to clinical response to a maximum of 2mg/kg/day.	• The mean final dose of atomoxetine for both studies was approximately 1.6mg/kg/day. • ADHD symptoms* were statistically significantly improved more on atomoxetine than on placebo.
2 identical adult studies (N=280, N=256)	• 10 week randomized, double-blind, placebo-controlled acute treatment studies. • Atomoxetine was administered as a divided dose, in the early morning and late afternoon/early evening. The dose was titrate to clinical response in a range of 60 to 120 mg/day.	• Mean final dose of atomoxetine for both clinical studies was approximately 95 mg/day. • ADHD symptoms in both studies were statistically significantly improved on atomoxetine**.

*measured with the ADHD Rating Scale-IV-Parent Version (ADHDRS) scale
** measured with Conners Adult ADHD Rating Scale Screening version (CAARS)

Adverse Effects[1]

Contraindications:

- Known hypersensitivity to atomoxetine or other constituents of the product.
- Concomitant use with, or within 2 weeks after discontinuing a monoamine oxidase inhibitor (MOAI)
- Narrow angle glaucoma. In clinical trials, Strattera™ use was associated with an increased risk of mydriasis.

Adverse Reactions: (*as reported in the product labeling*)

Common Treatment-emergent Adverse Events Associated with the Use of Strattera™ in Acute (up to 9 weeks) Child and Adolescent Trials*

Adverse Event	Percentage of Patients Reporting Events from BID Trials		Percentage of Patients Reporting Events from QD Trials	
	Strattera (N=340)	Placebo (N=207)	Strattera (N=85)	Placebo (N=85)
Upper abdominal pain	20	16	16	9
Constipation	3	1	0	0
Diarrhea	3	6	4	1
Dyspepsia	4	2	8	0
Nausea	7	8	12	2
Vomiting	11	9	15	1
Fatigue	4	5	9	1
Mood swings	2	0	5	2
Ear Infection	3	1	nr	nr
Influenza	3	1	nr	nr
Weight Decreased	2	0	nr	nr
Appetite decreased	14	6	nr	nr
Dizziness (except vertigo)	6	3	nr	nr
Headache	27	25	nr	nr
Somnolence	7	5	nr	nr
Crying	2	1	nr	nr
Irritability	8	5	nr	nr
Cough	11	7	nr	nr
Rhinorrhea	4	3	nr	nr
Dermatitis	4	1	nr	nr

*Table adapted from source 1
nr = not reported

Common Treatment-Emergent Adverse Events Associated with the Use of Strattera™ in Acute (up to 10 weeks) Adult Trials*

Adverse Event	Percentage of Patients Reporting Event	
	Strattera (N=269)	Placebo (N=263)
Palpitations	4	1
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Sinusitis	6	4
Weight decreased	2	1
Appetite decrease	10	3
Myalgia	3	2
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	16	8
Paraesthesia	4	2
Sinus headache	3	1
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Urinary hesitation and/or urinary retention and/or difficulty in micturation	8	0
Dysmenorrhea[1]	7	3
Ejaculation failure and/or ejaculation disorder[2]	5	2
Erectile disturbance[2]	7	1
Impotence[2]	3	0
Menses delayed[1]	2	1
Menstrual disorder[1]	3	2
Menstrual irregular[1]	2	0
Orgasm abnormal	2	1
Prostatitis[2]	3	0
Dermatitis	2	1
Sweating increased	4	1
Hot flashes	3	1

*Table adapted from source 1
[1]Based on total number of females (Strattera, n=95; placebo, n=91)
[2]Based on total number of males (Strattera, n=174; placebo, n=172)

Atomoxetine can increase blood pressure and heart rate and should be used with caution in patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease.

Drug Interactions[1]

- Albuterol and other beta-2 agonists – concomitant administration with atomoxetine may potentiate the cardiovascular action of albuterol
- CYPD2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) - concomitant administration increases the AUC and C_{max} of atomoxetine. An atomoxetine dose adjustment may be necessary.
- Monoamine oxidase inhibitors – Concomitant use or use within 2 weeks discontinuation of an MAOI is contraindication. Serious, sometimes fatal reactions (hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and extreme mental status changes, such as delirium to coma) have been reported with other drugs that affect brain monoamine concentrations
- Pressor agents – atomoxetine should be used cautiously with pressor agents because of its effects on blood pressure

Dosage and Administration[1]

Initial Treatment

- Children and adolescents up to 70 kg body weight – Initial dose, 0.5 mg/kg. Increase after a minimum of 3 days to a total target daily dose of approximately 1.2 mg/kg given as a single daily morning dose or in 2 equally divided doses in the morning and late afternoon/early evening. Clinical benefit has not been demonstrated for doses higher than 1.2 mg/kg/day The total daily dose for children and adolescents should not exceed 1.4mg/kg or 100mg, or whichever is less.
- Dosing of children and adolescents over 70 kg body weight and adults – Initiate at a total daily dose of 40mg and increase after a minimum of 3 days to a target total daily dose of approximately 80 mg given as a single daily dose in the morning or in 2 equally divided doses in the morning and late afternoon/early evening. After 2 to 3 additional weeks, the dose may be increased to a maximum of 100mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses. The maximum total daily dose in children and adolescents over 70kg and adults is 100mg.

Maintenance/Extended Treatment

Pharmacological treatment of ADHD may be needed for extended periods. For extended treatment, periodic evaluation is recommended to evaluate long-term usefulness of the drug for the individual patient.

Cost Comparison (at commonly used dosages)

Drug	Daily Dose Range	AWP* per month
Strattera	20 mg – 80 mg	$188**
Adderall XR	10 mg – 30 mg	$78 - $156
Concerta	18 mg – 54 mg	$77 - $88
Dextroamphetamine SR	10 mg – 40 mg	$27 - $110

*Average Wholesale Price: Facts and Comparisons (Medi-Span), St Louis, MO; December 2002. Costs rounded to the nearest whole dollar

**Equal pricing for 10mg and 40mg tablets

Conclusion

Strattera™(atomoxetine) is a selective norepinephrine reuptake inhibitor and is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD). The exact mechanism of action is unknown, but it is may be related to the selective inhibition of the pre-synaptic norepinephrine transporter. Unlike other medications used to treat ADHD, Strattera™ is not considered a stimulant and is not a controlled substance. The effectiveness of Strattera™ in the treatment of ADHD has been established in randomized, double-blinded, placebo-controlled studies in children, adolescents and adults. Strattera™ can increase blood pressure and heart rate and should be used with caution in patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease. The total daily dose for children and adolescents should not exceed 1.4mg/kg or 100mg, or whichever is less. The maximum total daily dose in children and adolescents over 70kg and adults is 100mg. Pharmacological treatment of ADHD may be needed for extended periods. For extended treatment, periodic evaluation is recommended to evaluate long-term usefulness of the drug for the individual patient.

Recommendation(s)

It is recommended Staterra™ be available through on a clinical edit.

Approval Criteria

- Diagnosis equals ADD/ADHD
- Trial and Failure on stimulant

Denial Criteria

- Lack of approval criteria

References

1. Strattera. Eli Lilly and Company; Indianapolis, Indiana. 2002 December
2. CenterWatch Clinical Trials Listing Service. Drugs Approved by the FDA. Strattera. http://www.centerwatch.com/patient/drugs/dru813.html

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